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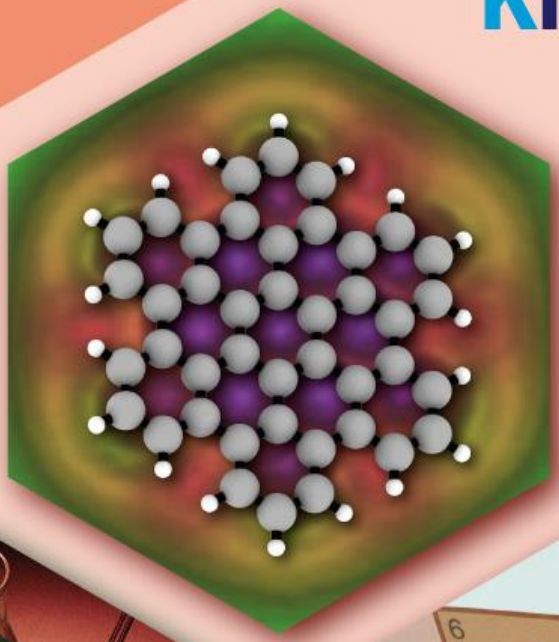

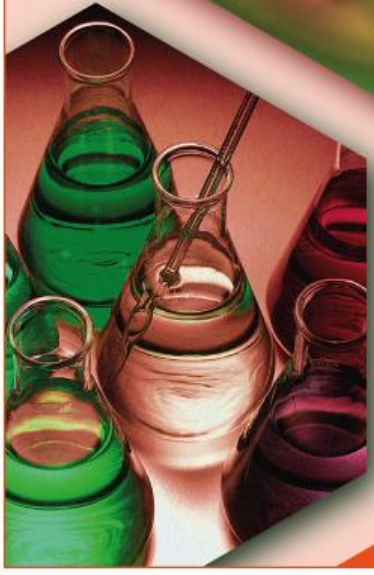

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Fluoroproline in MUC1 antigen opens a new via in the development of enhanced cancer diagnostic tools

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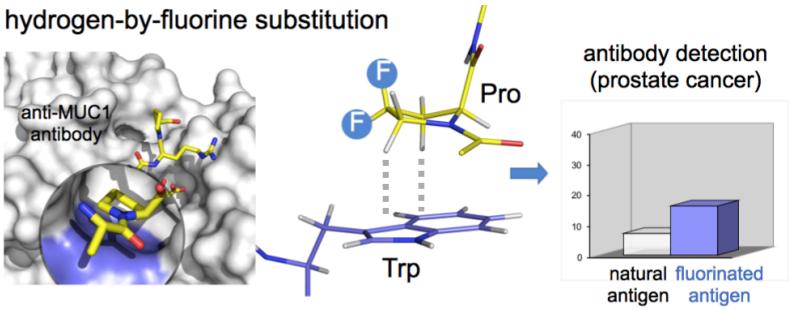
MUC1 is a glycoprotein overexpressed in around 80% of human cancers.[1] While in healthy cells, the MUC1 backbone displays complex oligosaccharides, in tumors it is decorated with basic, truncated carbohydrates. Consequently, different tumor-associated carbohydrate antigens (TACAs), such as the Tn determinant (α-O-GalNAc-Ser/Thr), become exposed and are involved in triggering immune responses.[2] Because of this unique feature, extensive efforts have been made toward the rational design of MUC1-based antigens to be used as diagnostic tools for detection of anti-MUC1 antibodies in human serum.[3]

In this work, a structure-based design of a new generation of tumor-associated glycopeptides with improved affinity against two anti-MUC1 antibodies is described. These unique antigens feature a fluorinated proline residue, such as a (4S)-4-fluoro-L-proline or 4,4-difluoro-L-proline, at the most immunogenic domain.[9] Binding assays using biolayer interferometry reveal 3-fold to 10-fold affinity improvement with respect to the natural (glyco)peptides. According to X-ray crystallography and MD simulations, the fluorinated residues stabilize the antigen−antibody complex by enhancing key CH/π interactions. Interestingly, a notable improvement in detection of cancer-associated anti-MUC1 antibodies from serum of patients with prostate cancer is achieved with the non-natural antigens, which proves that these derivatives can be considered better diagnostic tools than the natural antigen for prostate cancer.



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